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REVIEW

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Management of SARS-CoV-2 pneumonia

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has rapidly spread throughout the world since December 2019 to become a global public health emergency for the elevated deaths and hospitalizations in Intensive Care Units. The severity spectrum of SARS-CoV-2 pneumonia ranges from mild to severe clinical conditions. The clinical course of SARS-CoV-2 disease is correlated with multiple factors including host characteristics (genetics, immune status, age, and general health), viral load and, above all, the host distribution of the airways and lungs of the viral receptor cells. In this review, we will briefly summarize the current knowledge of the characteristics and management of coronavirus disease 2019-pneumonia. However, other studies are needed to better understand the pathogenetic mechanisms induced by SARS-Cov-2 infection, and to evaluate the long-term consequences of the virus on the lungs.

KEYWORDS
clinical presentation, COVID-19, pneumonia, SARS-CoV-2

1 | INTRODUCTION

Since December 2019, a new zoonotic beta-coronavirus (severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2])[1–4] has spread all over the world from Wuhan in China,[5,6] known as coronavirus disease 2019 (COVID-19). On January 30, 2020, the World Health Organization (WHO) declared a public health emergency and the epidemic rapidly evolved into a pandemic by the March 11, 2020, with a high number of cases in the European Region, especially in Italy.[7]

The phylogenetic analysis of SARS-CoV-2 showed that it was a Betacoronavirus, subgenus Sarbecovirus, 79% distant from SARS-CoV (2002–2003 epidemics) and 50% from MERS-CoV (2012 epidemic). The disease seems to have a zoonotic pathway of origin, as SARS-CoV-2 correlates with 88% identity to the two bat coronaviruses, bat-SL-CoVZC45, and bat-SL-CoVZXC21[8–10]; in fact, the bats were considered to be the hosts of the natural reservoir.

SARS-CoV-2 infection may lead to a wide range of clinical presentations, from an asymptomatic form to a severe acute respiratory syndrome: an asymptomatic infection may be present in up to 85% of confirmed cases[11]; among symptomatic patients, about 80% showed a mild clinical course, about 15% a severe and about 5% a critical disease,[12] especially as respiratory failure. The symptoms more frequently observed were fever, chills, myalgia, or fatigue, followed by a dry cough and dyspnea 3–7 days later.[13] Diarrhea or neurological symptoms (dysgeusia and/or anosmia) may be present 1–2 days before the development of fever and dyspnea.[14] Skin lesions have also been observed, especially in young people.[15] The time required for recovery ranges from 2 weeks in mild infections to 3–6 weeks in a severe disease.[16] The asymptomatic patients are usually young, have no comorbidities, and have an excellent prognosis, but >90% of these asymptomatic patients have radiological abnormal findings on diagnosis. Advanced age and presence of chronic comorbidities (cardiovascular disease, hypertension, diabetes, chronic lung, kidney, and cerebrovascular disease, or malignancy) have been considered the major risk factors for acute respiratory distress syndrome (ARDS) and mortality in SARS-CoV-2 patients.[14,17–19]

In this review, we will briefly summarize the current knowledge of the characteristics and management of COVID-19-pneumonia.

2 | PATHOGENESIS OF ACUTE LUNG INJURY IN SARS-COV-2 PNEUMONIA

The severity spectrum of SARS-CoV-2 pneumonia ranges from mild to critical conditions and the clinical course of the disease depends on multiple factors including host features (genetics, immune status, age, and general health), viral load, and, most relevantly, the host distribution of the airways and lungs of the viral receptor cells.[20–22]

SARS-CoV-2 enters the human cells through the angiotensin-converting enzyme 2 receptor (ACE-2).[23] This receptor is expressed on types I and II alveolar cells, lung endothelium and in heart, kidneys, liver, intestine, and other tissues. The overexpression of ACE-2 has been associated with pulmonary hypertension, sarcoidosis, idiopathic pulmonary fibrosis, and ARDS: ACE-2 could play a counter-regulatory role that may be crucial in the development and progression of acute lung failure. ACE-2 is a type I membrane protein; its physiological enzymatic activity on angiotensin I (Ang I) induces the production of Ang 1–9[24] and is involved in vasoconstriction and blood pressure control in the context of the renin-angiotensin-aldosterone system; a decreased expression of ACE-2 seems to be related to cardiovascular diseases.[25] The role of ACE-2 in the pathogenesis of COVID-19-pneumonia is suggested by studies on the virus structure reporting a higher binding affinity to ACE2 for SARS-CoV-2 spike receptor-binding domain (RBD) compared to SARS-CoV and RBD.[26,27]

A prospective observational study on 76 subjects showed that the mean viral load of severe cases was about 60 times higher than that of mild cases, so the viral load may be a factor related to a worse prognosis.[28]

Severely ill patients may exhibit lymphopenia and interstitial pneumonia with high levels of inflammatory cytokines (cytokine storm) characterized by elevated concentrations of interleukin (IL)-2, IL-6, IL-7, IL-10, tumor necrosis factor alpha (TNF-α), G-CSF, IP-10, MCP-1, and MIP-1α. The massive cytokine release probably plays a significant part in the induction of respiratory failure and ARDS. Some data support the evidence for hyperactivation of macrophages and monocytes and a resulting increase in neutrophils, IL-6, C-reactive protein, and a decrease in lymphocytes. Concerning the adaptive immune system, activation of the Th1/Th17 response might contribute to inflammation, while the production of specific antibodies by B-lymphocytes may be directed to neutralize the virus.[29]

In the pathogenesis of pneumonia, it is interesting to evaluate the dynamics of the antibody response, anti-SARS-CoV-2. Evidence from SARS-CoV and MERS-CoV infections indicate that in SARS-CoV infection immunoglobulin M could be detected in serum 3–6 days after disease onset and immunoglobulin (IgG) after 8 days while seroconversion in MERS-CoV infection occurs at the second or third week; for both types of coronavirus infection severe outcomes were observed in patients with a delayed and weaker antibody response.[29] On the contrary, an observational cohort study on 23 SARS-CoV-2 patients reported that serum antibody levels are not correlated with clinical severity, observing that deceased patients developed faster peak antibody anti-spike responses compared with recovered patients. Antispike IgG could cause immunopathological lung injury by binding Fcγ receptor on wound-healing macrophages.[30]

Finally, there is growing interest on the pathogenetic involvement of lung vascular coagulopathy in the respiratory failure of COVID-19 patients.[31–33] However, higher quality studies are needed to better understand and confirm the pathogenetic mechanisms induced by the SARS-Cov-2 infection.

3 | PATHOLOGY OF ACUTE LUNG INJURY IN SARS-COV-2 PNEUMONIA

Injury to the alveolar epithelial cells, hyaline membrane formation and hyperplasia of type II pneumocytes, consistent with diffuse alveolar damage, are the major findings at autopsy in patients who have died of SARS-CoV-2 pneumonia.[34,35] Histological examination may also show consolidation areas with fibroblastic proliferation, extracellular matrix and fibrin production in the airspaces (on some occasions consolidation was associated with intra-alveolar neutrophilic infiltration, suggestive of superimposed bacterial pneumonia); hyaline membrane formation was accompanied by vascular congestion; interstitial thickening caused by mononuclear inflammatory cell infiltration together with the presence of stromal cells and fibrin as well as hyperplasia of type II pneumocytes; fibrinoid necrosis involving the small vessels was also noted.[36]

Microvascular thrombosis and hemorrhage associated with alveolar and interstitial inflammation together with micro thrombosis in other tissues has been reported.[31,37–39]

4 | PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF SARS-COV 2 PNEUMONIA

4.1 | Pathophysiology

COVID-19 is a disease characterized by interstitial infiltrated pneumonia, which is fully within the definition of ARDS: it is an acute condition with severe hypoxemia and bilateral lung infiltrations not attributable to a left ventricular dysfunction. The particularity of these patients is that they retain good pulmonary compliance; they are hypoxemic but are “easily ventilable.” In most cases, the blood-gas analysis (ABG) analysis picture reveals hypoxemia with hypocapnia (respiratory failure type 1), often with tachypneic patients. The increase of the respiratory rate is attributable in part to the chemo-receptorial stimulus by hypoxemia, and in part to the stimulus of the J receptors.

Another important pathophysiological element seems to be the involvement of the vascular section, with diffuse endothelial damage and pulmonary vascular thrombosis, which causes in the

most severe forms an important deficit in the ventilation/perfusion ratio: some lung areas ventilate badly due to the presence of lung infiltration and/or interstitial edema, other areas ventilate well but are not regularly perfused due to the thrombotic occlusion of the vessels. The situation described above is the most critical, but fortunately many patients retain large areas of lung that ventilate well, or discreetly, and are well perfused.

4.2 | Clinical manifestations of SARS-CoV-2 pneumonia

The median incubation period was 5.2 (range: 2–14) days, during which transmission can occur.[4,40] The symptoms more frequently observed are fever, myalgia, chills and fatigue, followed by dry cough and dyspnea on average 3–7 days after COVID-19 contact, while nasal congestion, runny nose and sore throat are observed less.[12,13] Sometimes, palpitation, myalgia, headache, or diarrhea can precede respiratory symptoms. Aqueous diarrhea can be present in 10–25% of cases; vomiting, diarrhea, or abdominal pain in 25% of cases during the clinical course. A myocardial lesion, liver, and kidney injury and secondary bacterial infection may also be observed.[41] Cough and dyspnea appear a few days after the onset of symptoms.

Rodriguez-Morales in a meta-analysis including 19 studies with 2,874 patients observed that the clinical manifestations most frequently observed were fever (88.7%), cough (57.6%), dyspnea (45.6%), and with a lower frequency sore throat (11.0%), myalgia, or fatigue (29.4%), sputum production (28.5%), headache (8.0%), and diarrhea (6.1%). Laboratory findings resulting abnormal were lymphopenia (43.1%), leukopenia (18.7%), leukocytosis (16.8%), high C-reactive protein (CRP) (58.3%), high erythrocyte sedimentation rate (41.8%), high lactate dehydrogenase (57.0%), high AST (24.1%), high creatinine (4.5%) and decreased albumin (75.8%).[42]

The experience gained during these months has allowed us to stratify patients in clinical phenotypes different from each other for prognosis and clinical management; we describe the main clinical phenotypes and their possible clinical management:

1. Fever without respiratory insufficiency (normal ABG and walking tests) and RX normal chest: discharged with indication for auto quarantine pending the outcome of the swab.
2. Chest Rx, ABG, and fever indicative of outbreak and/or modest respiratory failure (PO_2 >60 mmHg, FiO_2 21%): O_2 therapy-hospitalization in ordinary hospital.
3. Fever with moderate to severe respiratory insufficiency documented by ABG in FiO_2 21% at the triage (PO_2 60 mmHg, FiO_2 21%): O_2 therapy/Continuous Positive Airway Pressure (CPAP)—hospitalization in ordinary hospital or subintensive unit (SIU).
4. Respiratory failure with suspected initial ARDS or complicated pneumonia: O_2 therapy /CPAP/orotracheal intubation (OTI) and invasive ventilation: hospitalization in SIU or IC.
5. ARDS as first sign: CPAP/OTI and invasive ventilation—hospitalization in SIU or IC.

5 | IMAGING LUNG ABNORMALITIES

The contribution of chest imaging in COVID19 diagnosis and management is fundamental.

5.1 | Chest X-ray

Consolidations are the most frequent manifestations on chest radiography, usually having a bilateral distribution and prominent involvement of the lower lobe.[43] Other results reported are nebulous radiopacity.[43]

5.2 | High resolution computed tomography

Chest high resolution computed tomography (HRCT) allows a detailed definition of pattern, distribution, and extension of COVID-19 pneumonia. The most frequently described chest computerized tomography (CT) abnormalities are ground-glass opacities (GGO), consolidations, GGO in combination with consolidative opacities, crazy-paving pattern and interstitial thickening or reticulation pattern; pleural involvement with pleural effusion and lymphadenopathy are infrequently observed. The reversed halo sign is referred to in a few studies.[43,44] Lesion distribution is mainly bilateral, peripheral and subpleural with a predilection for the lower lobes.

In the first 14 days from the onset of symptoms, GGOs is the most common pattern that can gradually progress and overlap with consolidations and crazy paving areas. The maximum extent of the lesions is reached at 10–11 days after symptom onset. A gradual resolution or residual patchy fibrosis up to 4 weeks is described, but the long-term persistence of residual lesions is currently unknown. In critical cases, the lesions may progress to “white lung” and acute ARDS.[44]

CT semi-quantitative and quantitative scoring methods to estimate the proportion of GGO and consolidation have also been proposed. The quantitative method appears to correlate well with the conventional semiquantitative method and laboratory indexes, and therefore may help the clinician to predict the severity of the SARS-CoV-2 pneumonia.[45]

5.3 | Lung ultrasound

Lung ultrasound (LUS) may have an important role in daily management of SARS-COV-2 patients with pneumonia because it allows a noninvasive assessment without radiation exposure. It is a dynamic observation of the lung and pleural line, a simpler and safer management than chest X-ray and especially HRCT. A disadvantage of LUS is the lack of a “panoramic view” of the chest and the impossibility of peri-hilar lesion visualization.[46,47]

Typical imaging features include B line patterns (focal, multifocal, and confluent) due to interlobular septa thickening, hazy opacities, or

subpleural consolidations and thickened pleural line. The lesion distribution is typically bilateral and multifocal.[45] The diagnostic efficacy of bedside LUS seems higher in severe disease cases than the mild ones[46] but could be useful to detect early lung involvement during the paucisymptomatic phase in confirmed cases.

Semiquantitative ultrasound methods to score lung involvement have been proposed in the past, for example, to monitor ventilated patients in intensive care unit (ICU) settings.[47] Soldati et al[48] proposed a similar scoring method for SARS-CoV-2 scanning 14 areas of the patient's chest (three posterior, two lateral, and two anterior) with a standard sequence of evaluations; a score from zero to three is assigned to each evaluated area.[48]

6 | TREATMENT OPTIONS

From the data acquired so far, we know that SARS-CoV-2 may evolve in two phases: a first viremic phase, likely to occur in the first week of the infection, and a second phase in which viremia decreases, while the systemic inflammatory state increases in response to many inflammatory stimuli, in particular in the pulmonary system. These phenomena lead some patients to a hyper-inflammatory condition, the so-called "cytokine storm," which occurs 1–2 weeks after the infection.

Considering the natural history of SARS-CoV-2 infection, antiviral therapy may be potentially effective in the first phase, whereas antiinflammatory drugs should be the milestone of treatment in the second phase.

6.1 | Antiviral drugs

The experience with SARS and MERS infections has provided valuable insights into potential pharmacological therapy in the ongoing SARS-CoV-2 pandemic. Several agents with apparent in vitro and in vivo activity against SARS-CoV and MERS-CoV have been proposed as potential candidates for SARS-CoV-2 treatment, even though the clinical benefits of none of these regimens have been demonstrated. The life cycle of SARS-CoV-2 identifies many steps, which may be potential targets for antiviral drugs: viral entry to host cells, viral polyprotein production and viral replication. The clinical disease staging proposed by Siddiqi et al[49] may play a significant role in choosing the right timing of treatment.[49]

Chloroquine (CQ) and hydroxychloroquine (HCQ), used to treat and prevent malaria and chronic inflammatory diseases, block the entry of SARS-CoV-2 into the host cells by inhibiting the glycosylation of the host receptors, the proteolytic processing and endosomal acidification. Moreover, an immunomodulatory effect has been described for both drugs, thanks to the reduction in cytokine production and the inhibition of autophagy and lysosomal activity in host cells.[50–56] Although there is no evidence to support the efficacy of HCQ or CQ therapy against SARS or MERS infections,[57,58] in vitro studies have demonstrated that both these agents decreased viral replication of SARS-CoV-2 in a concentration-dependent manner.[59] Several retrospective observational studies aimed at describing the efficacy of CQ or HCQ against SARS-COV-2 have been conducted with controversial results. A recent retrospective observational study compared 811 hospitalized patients who received HCQ (600 mg twice on day 1, then 400 mg daily for a median of 5 days) with 565 patients who did not. Patients receiving HCQ were more severely ill at baseline than those in the control group.[60] No significant association between HCQ and a lower risk of intubation or death was observed, even after a propensity score adjusted analysis (hazard ratio: 1.04; 95% confidence interval: 0.82–1.32). Moreover, a multinational registry analysis (ie, 671 hospitals in six continents) has recently been published with surprising results regarding the use of HCQ or CQ, with or without a macrolide, in hospitalized patients with COVID-19.[61] The registry included 96,032 patients with a positive laboratory finding for SARS-CoV-2. Of these, 14,888 subjects were included in the treatment group (1868 patients treated with CQ, 3783 with CQ plus a macrolide, 3016 with HCQ and 6221 with HCQ with a macrolide) and started the therapy within 48 h from the diagnosis, whereas 81,144 patients were included in the control group. The authors reported that chloroquine and HCQ, alone or in combination with a macrolide, were independently associated with both a higher in-hospital mortality rate compared to the control group and an increased risk of ex-novo ventricular arrhythmia compared to the control group (0.3%).[61] However, since these results have raised several concerns, the paper has been retracted from the authors.

Nevertheless, HCQ arm has been recently ceased in two large randomized control trials, Solidarity trial by WHO[62] and Recovery trial by the Oxford University in UK,[63] because of the lack of its efficacy in a cohort of hospitalized patients with COVID-19.

As well, the DisCoVeRy trial, a multicentre, adaptive, randomized open clinical trial, aiming to evaluate clinical efficacy and safety of four treatment arms (remdesivir, LPV/r, interferon-beta 1A, HCQ) in addition to the usual standard of care, has temporarily stopped the HCQ arm since the 24th of May 2020.[64,65]

Lopinavir/ritonavir (LPV/r) is an oral combination agent approved for the treatment of HIV infection; LPV is a protease inhibitor and ritonavir a booster of LPV by inhibiting cytochrome P450. Studies in vitro have demonstrated an antiviral activity of LPV against SARS-CoV and MERS-CoV through the inhibition of 3-chymotrypsin-like protease.[66–69] Choy et al[70] reported an antiviral effect of LPV but not ritonavir against SARS-CoV-2 in vitro.[70] There are few clinical studies regarding LPV/r activity against human coronaviruses, mostly conducted on SARS-CoV-1 infection, with promising results.[67,71] One study demonstrated that the combination LPV/r and ribavirin had a synergistic effect for the treatment of SARS, in the early phase of infection.[71]

Reports regarding LPV/r activity against SARS-CoV-2 mostly derive from case-reports or small nonrandomized, retrospective studies, with controversial results. Therefore, they do not allow the direct efficacy of LPV/r to be asserted against SARS-CoV-2.[72] Recently, Wang et al[73] evaluated the efficacy of LPV/r compared to the

standard of care in 199 patients hospitalized with severe SARS-CoV-2, without significant differences in time to clinical improvement or in 28-day mortality rate or in viral clearance. However, LPV/r was administered late during SARS-CoV-2 infection, at a median of 13 days from the onset of symptoms.[73] Nevertheless, in a subgroup analysis among patients who started LPV/r within 12 days from symptom onset, colleagues found no significant difference in clinical improvement.[73] Thus, the timing of administration of antiviral agents seems crucial: the initiation of LPV/r beyond the peak viral replication phase (initial 7–10 days) had no effect on the clinical outcomes.[71,72] Other randomized control trials (RCTs) are evaluating the role of LPV/r in SARS-CoV-2 infection. For example, the DisCoVeRy trial, a multicentre, adaptive, randomized open clinical trial, aiming to evaluate clinical efficacy and safety of 4 treatment arms: remdesivir, LPV/r, Interferon-beta 1A, HCQ in addition to the usual standard of care.[64]

Nevertheless, the Recovery trial by Oxford University in UK has recently described no clinical benefit from use of LPV/r in hospitalized patients with COVID-19.[64] As a matter of fact, colleagues found no significant difference in the 28-day mortality between 1596 patients treated with LPV/r and 3376 patients randomized to usual of care alone (22.1% LPV/r vs 21.3% usual of care) nor in the risk of progression to mechanical ventilation or length of hospital stay.[64] However, these results may not be applied to severe patients with COVID-19 requiring invasive ventilation, because they could not study a large number of patients on mechanical ventilation.

Other protease inhibitors, such as darunavir/cobicistat (DRV/c) or/ritonavir have been identified as potential agents with activity against SARS-CoV-2 infection, thanks to the mechanism of action of DRV, similar to LPV.[73] DRV/c is a fixed combination of a protease inhibitor, DRV, and a CYP3A4 inhibitor, cobicistat, indicated for the treatment of HIV infection. In vitro cell models have demonstrated a significant activity of DRV/c against SARS-CoV-2.[74] However, few data regarding the efficacy and safety profile of DRV/c against COVID-19 are available.

Remdesivir, officially known as GS-5734, is a nucleotide analogue, a prodrug that mimics adenosine and causes premature termination of viral RNA replication by inhibition of viral RNA-dependent RNA polymerase, which was originally developed against Ebola virus infection. It has shown a broad antiviral spectrum against different RNA-viruses, such as coronaviridae and flaviviridae. Potent in vitro and in-human cell activity was demonstrated against MERS-CoV and SARS-CoV.[75] Recent results from in vitro and in vivo studies have shown that remdesivir has potent antiviral activity against SARS-CoV-2.[76–78] In a multicenter, multinational series, 53 patients with severe SARS-CoV-2 received the antiviral drug on a compassionate-use basis for up to 10 days: 68% of them (36/53) had a clinical improvement and of the 30 patients who were mechanically ventilated at baseline 17 (57%) were extubated.[79] A randomized, double blind, placebo-controlled multicenter trial randomized 236 patients with moderate SARS-CoV-2 in a 2:1 ratio either to remdesivir (200 mg 1st day and then 100 mg for 9 days) or placebo and showed no significant difference between the two groups in the time of clinical improvement nor in 28-day mortality.[80] However, remdesivir was associated with a faster time to clinical improvement among patients treated within 10 days from the onset of symptoms, although not statistically significant. Furthermore, in this study remdesivir did not result in a significant reduction in SARS-CoV-2 RNA viral loads in the upper respiratory tract despite the strong antiviral effects in preclinical models.[80] Lastly, the preliminary report of a double-blind, randomized, placebo-controlled trial was recently published showing encouraging effects of remdesivir in hospitalized adults suffering from COVID-19 with involvement of lower respiratory tract.[81] Of the total 1059 patients, 538 were assigned to the remdesivir group and 521 to placebo. The study arm showed a lower median recovery time (11 vs. 15 days, $p < .001$) and a lower mortality rate than 14 days (7.1 vs. 11.9%).

Another ongoing RCT evaluating efficacy and safety of remdesivir is the DisCoVeRy trial.[64]

On the 1st of May 2020, the US Food and Drug Administration (FDA) has authorized emergency use of remdesivir, for the treatment of hospitalized patients with suspected or confirmed severe COVID-19.[82]

Hence, due to its properties, remdesivir is the best candidate for SARS-CoV-2 treatment.

Several other randomized trials are underway to evaluate the effectiveness of remdesivir against SARS-CoV-2 infection.[83–89]

Although numerous studies have been conducted, their controversial results cannot provide data on the efficacy of these agents against SARS-CoV-2.

At present, there is no high-quality evidence to support any of the treatments currently proposed to improve the clinical outcome. The main international scientific societies (WHO; International Society of Infectious Diseases—IDSA; Centers for Disease Control and Prevention—CDC; National Institute of Health—NIH) recommend that patients should be treated in the context of a formal clinical trial.[90,91] Additional RCTs are needed to establish the safety, efficacy, harm, and benefit of agents against SARS-CoV-2 infection.

6.2 | Adjunctive therapies

Due to the lack of evidence regarding antiviral agents, the mainstay of SARS-CoV-2 treatment remains supportive therapies, including several interventions: from drugs for symptomatic relief to O_2 therapy to intensive care support. However, adjunctive therapies, such as corticosteroids and immunomodulatory agents, are gaining increasing interest, especially in the second phase of infection. In the phase of cytokine storm high inflammatory parameters, including CRP and proinflammatory cytokines (IL-6, TNF-α, IL-8, etc), are evident, and vasculitis, hypercoagulability and damage to multiple organs can occur. Considering this deterioration, it is reasonable to try to stop this cytokine storm. Markers such as PaO_2/FiO_2 index <250 mmHg and CRP, IL-6, IL-1, D-dimer should be considered to decide the use of antiinflammatories.

Although no antiinflammatory treatment has been approved by the FDA or EMA for SARS-Cov-2 treatment, there are clinical reports in the literature and several clinical investigations are ongoing. Among these, glucocorticoids, immunosuppressants, inflammatory cytokine antagonists (such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, and inhibitors of the Janus kinase pathway [JAK]) are objects of interest.

6.3 | Corticosteroids

Benefits of corticosteroids in COVID-19 remain a matter for debate.[92–94]

Previous studies on SARS and MERS patients documented a reduction in viral RNA clearance in patients treated with corticosteroids, with no difference in mortality.[95] In patients with influenza pneumonia, corticosteroid use is associated with a higher mortality.[96] In a prospective cohort study that enlisted 2141 patients with influenza A viral pneumonia (H1N1),[97] low/moderate doses of corticosteroids (25–150 mg/day methylprednisolone) were shown to reduce mortality in patients with a Sao_2/Fio_2 ratio of 300 mmHg.

On the basis of these studies and due to the lack of evidence the WHO advises against the use of corticosteroids in COVID-19 pneumonia, whilst considering the possibility of studies on steroids as an additional therapy.[98] In patients with severe COVID-19 but without ARDS, direct evidence from two observational studies provided very low-quality evidence of an increase in mortality with corticosteroids.[99] However, an observational study of 84 patients with COVID-19 and ARDS suggested that corticosteroid therapy can reduce mortality by 15% and the duration of mechanical ventilation.[100]

Russell et al[101] have highlighted the potential bias on publications assessing the effectiveness of corticosteroids on SARS-Cov-2 respiratory pathology, where the use of corticosteroids had been reserved only for the most critical patients. According to Russell et al,[101] such nondefinitive clinical evidence is not a sufficient reason to abandon the use of corticosteroids in SARS-CoV-2 pneumonia. In fact, other studies have positively evaluated the use of corticosteroids when administered at low or moderate doses in patients with coronavirus.[100,102] A Chinese study[100] observed a favorable effect of methylprednisolone in 201 SARS-CoV-2 patients with ARDS.

The guidelines on the Management of ARDS[103] of the Faculty of Intensive Care Medicine and the Intensive Care Society suggested the administration of methylprednisolone to patients with moderate to severe early ARDS (1 mg/kg/day). Methylprednisolone should be weaned slowly (6–14 days) and not quickly (2–4 days) or abruptly as a deterioration may occur from the development of a reconstituted inflammatory response. Similarity between SARS-CoV-2 and ARDS from other multifactorial pathologies suggests that it is reasonable to apply the same antiinflammatory approach also during severe COVID-19 pneumonia. Recent preliminary results from the RECOVERY trial strongly suggest that low dose dexamethasone reduces deaths in ventilated COVID-19 patients, as well as reducing deaths by one fifth in patients treated with oxygen; no benefit was observed in milder disease.[104]

6.4 | Tocilizumab

Clinical studies have shown increased levels of cytokines in patients with COVID-19 pneumonia, particularly of IL-6 (but also of IL-1, IL2, IFN-gamma, TNF-α, and IL-10) and that high levels of IL-6 correlated with the severity of the disease.[105]

Tocilizumab (TCZ) is a recombinant human monoclonal IL-6 antibody, which binds to soluble and membrane-bound IL-6 receptors blocking IL-6 signaling and mediated inflammatory response. TCZ is approved for treatment of rheumatic diseases, rheumatoid arthritis and for severe life-threatening cytokine release syndrome caused by T-cell immunotherapy of the chimeric antigen receptor. Xiaoling et al[106] administered alone TCZ (400 mg once iv) in 20 Chinese patients with SARS-CoV-2 pneumonia, and temperature returned to normal, oxygenation improved (75%) and opacity of lung injury in CT scans resolved (90.5%). Several studies evaluating the safety and efficacy of TCZ in the treatment of severe SARS-CoV-2 pneumonia are ongoing.[107–116]

Treatment consists of a single dose of 8 mg/kg (up to a maximum of 800 mg/dose) and a second dose equal to the previous one can be administered after 12 h in case of failure and a third dose after 24–36 h.

Among the possible side effects of TZV in the treatment of SARS-CoV-2 are osteonecrosis of the mandible,[106] upper airway infections, hypercholesterolemia, leukopenia, neutropenia, abdominal pain, oral ulcers, gastritis, peripheral edema, hypersensitivity, interstitial pneumonia, coughing, wheezing, conjunctivitis, increased liver transaminase, headache, dizziness, hypertension, rash, itching and hives.

6.5 | Eculizumab

Eculizumab is a humanized IgG monoclonal antibody, produced with recombinant DNA technology, which inhibits terminal complement. After binding to the complement C5 protein, it blocks its enzymatic cleavage into C5a and C5b and prevents the formation of the terminal complement C5b-9 complex.[117]

After multiple doses, a steady state is reached after about 49–56 days.[117] The possible side effects associated with the use of eculizumab are headache and infections (particularly rhino-pharyngeal and herpetic). Treatment with eculizumab simulates hereditary deficiency of terminal complement factors and may increase the susceptibility of the patient to infections sustained by capsulated pathogens, particularly meningococci.

Since the evidence of cytokine storm, eculizumab has been used in SARS-CoV-2 pneumonia with promising results in four patients admitted to the ICU for severe pneumonia and ARDS in Naples.[118] However, research has been conducted on too few patients and

further studies are needed to define the effectiveness and safety of the drug in this setting.[117,118]

6.6 | Anakinra

Anakinra is a recombinant form of the human interleukin 1 receptor antagonist protein (IL-1Ra), secreted in the human body by tissue monocytes and macrophages, modulating the innate immune response; blocking the IL-1 receptor inhibits the inflammatory responses.[119] Therefore, the similarities observed between the "cytokine storm" of severe sepsis and SARS-CoV-2 severe pneumonia suggest anakinra may be a potential therapeutic tool for patients with severe SARS-CoV-2 pneumonia. In a recent study (Ana-COVID), authors found that Anakinra reduced both the need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19, without serious side-effects.[120–123]

6.7 | Acalabrutinib

Acalabrutinib is a selective Bruton tyrosine kinase (BTK) inhibitor approved to treat several blood cancers. BTK regulates macrophage signaling and activation. Based on the possibility that BTK inhibitors may modulate human inflammatory responses dominated by macrophages, a prospective off-label clinical study has recently been performed by Roschewski et al.[124]

Acalabrutinib was administered to 19 patients hospitalized with severe COVID-19 (11 on supplemental oxygen; eight on mechanical ventilation): improved oxygenation in the majority of patients was observed without major toxicity; normalization of C-reactive protein and IL-6 occurred quickly in the majority of patients, as well as lymphopenia. Most (72.7%) patients on supplemental oxygen were discharged on room air, 50% of mechanically ventilated patients were successfully extubated, with 25% of them discharged on room air. Based on these results Acalabrutinib has the potential to be a candidate in the treatment of COVID-19. However, larger studies are required.

6.8 | JAK pathway inhibition

JAK inhibition may modulate both inflammation and cellular viral entry in SARS-COV-2. Richardson et al[125] observed that apart from ACE2, to infect lung cells SARS-CoV-2 uses also lung AT2 alveolar epithelial cells. One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might interrupt the passage of the virus into the cells and the intracellular assembly of virus particles. Of 378 AAK1 inhibitors in the knowledge graph, 47 have been approved for medical use and six inhibited AAK1 with high affinity. One of the six high-affinity AAK1-binding drugs was the JAK inhibitor, baricitinib, which also binds the cyclin G-associated kinase, another regulator of endocytosis. However, no data are available in the literature in patients with COVID-19-pneumonia.

7 | CONCLUSIONS

Despite numerous studies in the literature, there is currently no consensus in the scientific community on the treatment of COVID-19 pneumonia. As regards antiviral therapy, we are waiting for the results of several ongoing trials. As regards the use of antiinflammatory drugs in the fight against SARS-CoV-2 pneumonia, the efficacy, best timing, the candidate patients, and contraindications are still being evaluated.[126,127]

Results from several ongoing trials on antiviral therapy are awaited. The efficacy, best timing, patient selection and contraindications are still being evaluated in use of antiinflammatory drugs. A major concern regarding antiinflammatory drugs, such as corticosteroids, is delayed elimination of Sars-Cov-2 and the increased risk of a secondary infection, especially in immunosuppressed patients. However, the cytokine storm linked to the subject's immune response, in the absence of corticosteroid therapy, may cause much more severe and rapidly progressive pneumonia.

The concern for monoclonal antibodies directed against proinflammatory cytokines lies in the fact that they can inhibit a single inflammatory factor, but since many biological factors contribute to determining the inflammatory cascade, these drugs may or may not be as effective as expected or only for selected patients. It is also true that some antiinflammatory drugs such as JAK inhibitors also inhibit the production of interferon-α, which has an antiviral effect and could therefore reduce the efficiency of the body's response to infections. Untangling these uncertainties is one of the main research objectives in the near future.

However, waiting for efficacious treatment, we underlined that the role of asymptomatic subjects in the dissemination of SARS-CoV-2 infection is essential and so their identification is today the most important mechanism to stop the spread of the virus,[128-131] about 23% of infected people never developed symptoms in a China study.[130]

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Nicola Coppola, Andrea Bianco, and Caterina Sagnelli were involved in review concept, design, and critical revision for important intellectual content.

Benito Celia, Caterina Monari, Giulia De Angelis, Salvatore Cirillo, and Vanvitelli COVID-19 group: SD, MS, GS, AC, SM, MM, FC, AR, VG, CC, GM, RA, ID MN, SB, VC, MC, MD, MD, GM, MM, FFM, GP, RR, GS, and NV performed the literature search and drafted the manuscript.

Nicola Coppola, Caterina Sagnelli, and Andrea Bianco were involved in the critical revision of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

DESCRIPTION OF A CLINICAL CASE

We observed a 79-year-old-Caucasian woman with severe SARS-CoV-2 pneumonia, successfully treated with TCZ. The patient, with a history of idiopathic arterial hypertension, presented dry cough and fever (38.0°C). A nasopharyngeal-oropharyngeal SARS-CoV-2 swab resulted positive at 7 days from the onset of symptoms. On admission lung CT scan showed interstitial bilateral pneumonia, multifocal GGO, a LUS reaeration score of five and FiO_2 21% (PaO_2/FiO_2 437 mmHg). Hydroxycloroquine (400 mg bid the 1st day and then 200 mg bid) and LPV/r (200/5 mg 2tb bid) and low molecular weight heparin (LMWH, 4000 UI/die) were administered. After 4 days, the patient was afebrile with stable clinical parameters. At 11 days after the onset of symptoms, the patient developed fever (38.5°C), dyspnea (respiratory rate-RR 32), deterioration of arterial blood gas analysis (PaO_2/FiO_2 270 mmHg), D-dimer values 5.1 times higher than normal, and CRP 17.1 times was observed. CT showed an increased extension of GGO in both lobes with parenchymal consolidations, and a LUS score of 11. TCZ (8 mg/kg) intravenous therapy was administered. After 24 h blood gas analysis showed PaO_2/FiO_2 135.6 mmHg and a second dose of TCZ (8 mg/kg) was administered iv, followed by methylprednisolone (1 mg/kg/die). Over the next few days, biochemical and clinical signs improved. A drug-correlated reduction in platelets (34×10^3/ul) resolved within 7 days (platelets 94×10^3/ul). The patient was discharged in good clinical condition with two negative nasopharyngeal swabs, and a LUS of two at 30 days since the onset of symptoms.

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